DAC

PATENT APPLICATION

1647

#23

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Boyle, William J.		
Serial No.:	09/211,315	Group Art Unit No.:	1647
Filed:	December 14, 1998	Examiner:	Turner, S.
For:	Osteoprotegerin Binding Proteins		
Docket No.:	A-451J		

PETITION UNDER 37 CFR 1.181

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Pursuant to 37 CFR 1.181(a), Applicant hereby petitions to withdraw as premature a final rejection and requests that the application be reinstated as a pending application.

The statement of facts is as follows:

1. On January 3, 2001, an Office Action for U.S. Serial No. 09/211,315 was mailed in which pending Claims 37-49 were rejected. A copy of the Office Action is attached hereto as Exhibit A.

2. On June 28, 2001, a Fee Authorization/Amendment Transmittal Letter requesting a three month extension of time and a Response was mailed by Applicant. Copies of the Fee Authorization/Amendment Transmittal Letter and the Response are attached hereto as Exhibit B.

3. On July 31, 2001, an Advisory Action was mailed indicating *inter alia* that the proposed amendments were not entered, the rejections were maintained, and that the application was not in condition for allowance. A copy of the Advisory Action is attached hereto as Exhibit C.

4. On August 14, 2001, a Notice of Abandonment was mailed for failure to reply to the Office letter mailed on July 31, 2001. A copy of the Notice of Abandonment is attached hereto as Exhibit D.

EXPRESS MAIL CERTIFICATE

"Express Mail" mail labeling number: EL360688568US Date of Deposit: November 28, 2001

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, U.S. Patent and Trademark Office, P.O. Box 2327, Arlington, VA 22202.

Lynne Buchsbaum
Printed Name

Lynne Buchsbaum
Signature

As shown in Exhibit A, there was no indication in the Office Action that the rejections had been made final. The box in the Office Action Summary Form PTO-326 indicating a final action had been checked but appeared to have been subsequently "whited out" by the Examiner. In addition, the Office Action does not conclude with Form Paragraph 7.39 as set forth in the Manual of Patent Examining Procedures (MPEP 706.07) which states that the Office Action has been made final. Based on the absence of any indication that the action had been made final, Applicant maintains that the final rejection was premature and should be withdrawn. Moreover, Applicant maintains that mailings of an Advisory Action and a Notice of Abandonment were made in error based on the Examiner's allegation of a final rejection which was premature.

Applicant requests withdrawal of the final rejection and reinstatement of the application as a pending application. A response to the outstanding Office Action has previously been submitted.

This petition is being submitted more than two months after the mailing of the Advisory Action (the action complained of), which exceeds the period of time for filing a petition under 37 CFR 1.181(f). Applicant submits, however, that he has acted diligently and without intentional delay to seek withdrawal of the final rejection. Applicant's representative contacted the Examiner by telephone to request reconsideration of the action but no reconsideration was given, thus necessitating the filing of this petition. Applicant respectfully requests that the petition be granted.

The Commissioner is hereby authorized to charge the petition fee of $130.00 and any additional fees which may be required or credit any overpayment to Deposit Account No. 01-0519 in the name of Amgen Inc. An original and one copy of this paper are enclosed.

Respectfully submitted,

Robert B. Winter
Attorney/Agent for Applicant(s)
Registration No.: 34,458
Phone: (805) 447-2425
Date: November 28, 2001

Please send all future correspondence to:

U.S. Patent Operations/RBW
Dept. 4300, M/S 27-4-A
AMGEN INC.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

EXHIBIT A

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PATENT OPERATIONS
AMGEN

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trad mark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/211,315	12/14/98	BOYLE	W A-451-D

HM12/0103

US PATENT OPERATIONS/RBW
DEPT 430 M/S 27-4-A
AMGEN INC
ONE AMGEN CENTER DRIVE
THOUSAND OAKS CA 91320-1799

EXAMINER	
TURNER, S	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED:

OIPE JC17 NOV 28 2001 PATENT & TRADEMARK OFFICE

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DEC 03/01
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DOCKETED
3 mo. Resp. 4-3-01
6 mo. Resp. 7-3-01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/211,315	Applicant(s) B yle
	Examiner Shar n L. Turn r, Ph.D.	Group Art Unit 1647

☒ Responsive to communication(s) filed on *10-18-00*

This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *37-49* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *37-49* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *16*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

Response to Amendment

1. The Art Unit of U.S. Patent application SN 09/211,315 has changed. In order to expedite the correlation of papers with the application please direct all future correspondence to Examiner Turner, Technology Center 1600, Art Unit 1647.

Continued Prosecution Application

2. The request filed on 10-18-00 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/211315 is acceptable and a CPA has been established. An action on the CPA follows.

3. As a result of applicants amendment, all rejections not reiterated herein have been withdrawn by the examiner.

4. Claims 37-49 are pending.

Rejections Maintained

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 37-49 stand rejected under 35 U.S.C. 112, first paragraph, as set forth in Paper No. 8, mailed 6-8-99 as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant argues that the specification discloses the biological function of osteoprotegrin binding protein (OPGbp) and the effects of blocking OPGbp, that modulators of OPGbp activity which are either agonists or antagonists are readily identified by assays such as those described in Examples 8 and 9, that the application teaches OPGbp modulators and antibodies, that the specification teaches one skilled in the art how to obtain a modulator of OPGbp and to evaluate the properties of said modulator on in vitro and in vivo OPGbp activity, and that in particular the specification teaches the production of antibodies which bind OPGbp and identify either antibody agonists and antagonists of OPGbp activity.

These arguments have been considered but are not persuasive for the reasons made of record and as further discussed herein. Applicants have disclosed that OPGbp administration causes bone resorption in vivo. Osteoprotegrin (OPG) is recognized to promote bone formation. Applicants have shown that OPG administration decreases the amount of bone resorption seen after OPGbp administration. However, the claims recite a method of inhibiting bone resorption in a mammal comprising administering a modulator of an osteoprotegerin binding protein, wherein the modulator is an antibody or fragment thereof which binds an osteoprotegerin binding protein. The experiment, disclosed in Example 9 (*administration of OPG* to reverse the bone resorption effects seen in mice following administration of OPGbp), differs from the method claimed, *administration of an antibody which binds OPGbp*. There are no examples given in the specification whereby antibody to OPGbp is shown to modulate bone resorption. Takahishi et al, Biochem. and Biophys. Res. Comm., 256:449-55, 1999 teach that osteoclastic bone resorption

consists of two major processes: one is the recruitment of new osteoclasts and the other is the activation of mature osteoclasts, see p. 449, col. 1, lines 14-15, in particular. The specification does not teach that administration of an OPGbp antibody affects these processes. Ligand-receptor interactions are complex and the skilled artisan can not predict how the binding of an antibody to any ligand will enhance or inhibit the affinity or binding of that ligand to its receptor. In addition, one can not predict the altered signal properties of the receptor upon binding a ligand bound by an antibody. The method instantly claimed is not enabled because contrary to applicants assertion the specification has not taught how to identify, predict or screen for those antibodies which not only bind OPGbp, but modulate OPGbp activity such that bone resorption is inhibited. Applicants arguments appear to assume that all antibodies to OPGbp will bind to block the bone resorption activity of OPGbp, thus inhibiting bone resorption. However applicants fail to test this hypothesis and contrary to applicants assertion do not teach that an OPGbp antibody either in vitro or in vivo can exhibit anti-bone resorption activities. The administration of OPG (a decoy receptor, see Takahashi et al, Figure 1, 2) to animals does not aid the skilled artisan in determining those antibodies that will inhibit bone resorption from those that enhance bone resorption as a result of binding OPGbp. Applicants have not disclosed any antibodies which bind and act as either agonists or antagonists of bone resorptive activity. There are no antibodies utilized in Example 8 or Example 9. The only antibodies discussed in applicants specification are those hypothetically generated in Example 11, see specification, p. 47-51. Thus, in view of the quantity of experimentation necessary to identify those antibodies

which bind and inhibit bone resorptive activity, the lack of any working examples using such antibodies either in vitro or in vivo, the unpredictability of the art with respect to ligand-receptor and decoy receptor interactions, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> **A person shall be entitled to a patent unless --**
>
> **(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.**

8. Claims 37-38 are rejected under 35 U.S.C. 102(a) as being anticipated by Tsukii et al., Biochem. Biophys. Res. Comm., 246:337-41, 1998 as evidenced by Takahashi et al., Biochem. Biophys. Res. Comm., 256:449-55, 1999.

Tsukii et al., teach a method of inhibiting bone resorption in a mammal comprising administration of a osteoprotegerin binding protein (also known as osteoclast differentiation factor (ODF), see in particular identical structure as evidenced in Takahahi et al., Biochem. Biophys. Res. Comm., 256:449-55, 1999) polyclonal antibody, see in particular p. 337 abstract and p. 339, Figures 2-3 os Tsukii et al. Thus the reference teachings anticipate the claimed invention.

Status of Claims

9. No claims are allowed.

Conclusion

10. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached at (703) 308-4623.

Sharon L. Turner, Ph.D.
January 2, 2001

CHRISTINE J. SAOUD
PRIMARY EXAMINER
Christine J. Saoud

Sheet 1 of 1

Modified Form PTO-1449	Atty. Docket No. A-451J	Serial No. 09/211,315
LIST OF REFERENCES CITED BY APPLICANT (Use several sheets if necessary)	Applicant Boyle, William J.	
	Filing Date December 14, 1998	Group 1647

U.S. PATENT DOCUMENTS

EXAMINER'S INITIALS		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	A1						
	A2						
	A3						
	A4						
	A5						
	A6						
	A7						
	A8						
	A9						
	A10						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION YES	TRANSLATION NO
SV	B1	EP 0 911 342 A1	4/28/1999	Europe				
SV	B2	WO 97/23614	7/03/1997	PCT				
SV	B3	WO 99/29865	6/17/1999	PCT				
	B4							
	B5							

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

SV	C1	Tsukii et al, "Osteoclast Differentiation Factor Mediates an Essential Signal for Bone Resorption...", Biochemical and Biophysical Research Communications, 246, pp 337-341 (1998)
	C2	
	C3	
	C4	
	C5	
	C6	

EXAMINER: Susan Ungar Date Considered: 12-28-00

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

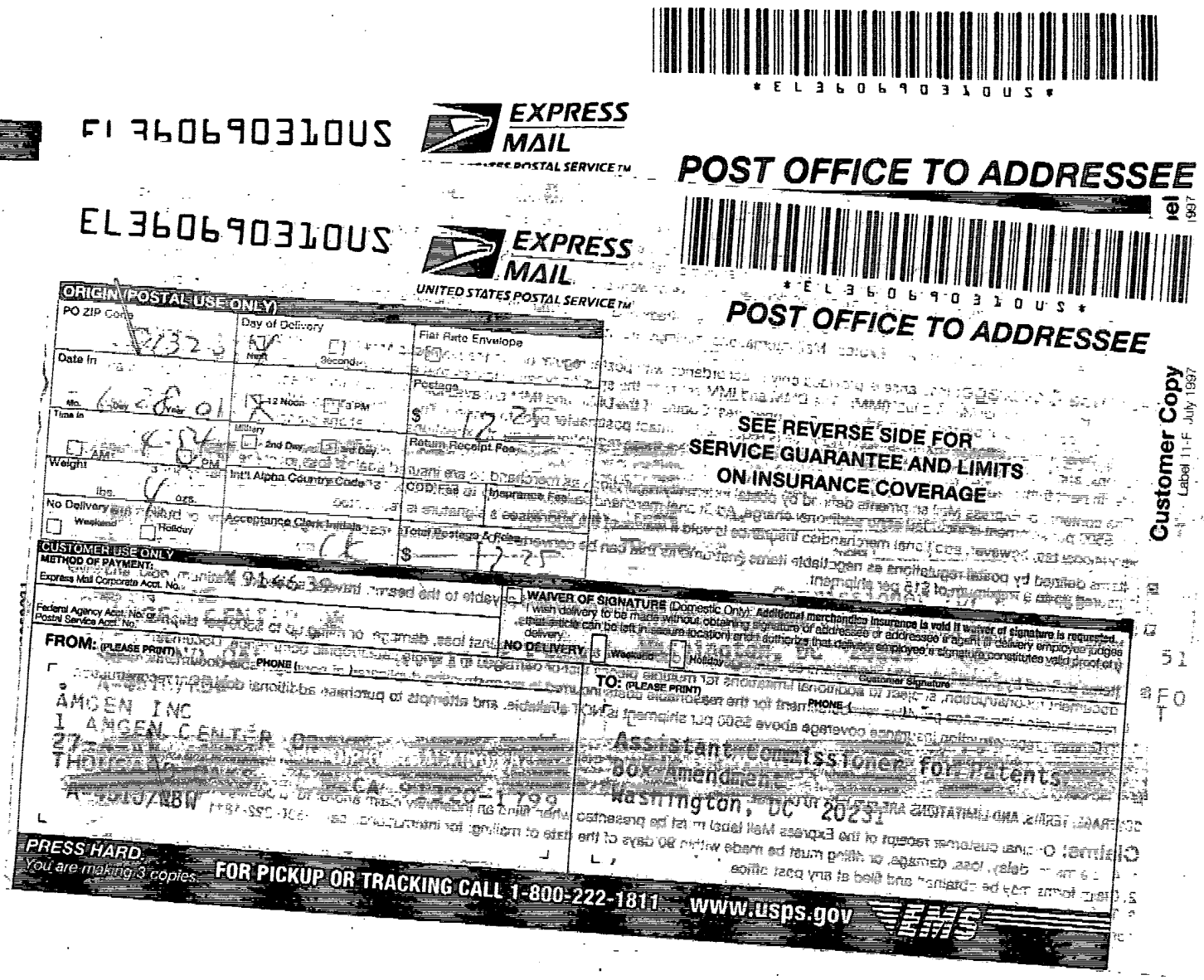
EXHIBIT B

THE PATENT OFFICE IS HEREBY REQUESTED TO ACKNOWLEDGE RECEIPT OF THE FOLLOWING DOCUMENTS BY DATE STAMPING AND RETURNING THIS POST CARD

Applicants: Boyle, William J.
Serial No.: 09/211,315
Filed: December 14, 1998
For: Osteoprotegerin Binding Proteins

* Fee Authorization / Amendment Transmittal Letter (1 page + 1 copy)
* Response and Amendment (9 pages)
* Exhibit A (2 pages)

A-451J/RBW
Express Mail, No. EL360690310US, on June 28, 2001



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Total Postage & Fees: $ 12.25

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NO DELIVERY: Weekend / Holiday

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AMGEN INC
1 AMGEN CENTER DR
THOUSAND OAKS CA 91320-1799
A-5010/NBW

Customer Signature:

TO: (PLEASE PRINT) PHONE (

Assistant Commissioner for Patents
Box Amendment
Washington, DC 20231

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EMS

PATENT APPLICATION

FEE AUTHORIZATION / AMENDMENT TRANSMITTAL LETTER			Attorney's Docket No: A-451 J
Serial No. 09/211,315	Filing Date December 14, 1998	Examiner Turner, S.	Group Art Unit 1647

In Re Application of
William J. Boyle

For
Osteoprotegerin Binding Proteins

TO THE ASSISTANT COMMISSIONER FOR PATENTS:

☒ Applicant(s) request(s) the following extension of time under 37 CFR 1.136(a):

- ☐ One month of original due date ($110.00)
- ☐ Two months of original due date ($390.00)
- ☒ Three months of original due date ($890.00)
- ☐ Four months of original due date ($1,390.00)
- ☐ Five months of original due date ($1,890.00)

☒ A response in connection with the matter for which this extension is requested:

- ☒ is filed herewith.
- ☐ has been filed.
- ☐ The response is the filing of a continuing prosecution application, the prior application having an express abandonment conditioned on the granting of a filing date to the continuing application.

☐ The accompanying papers include amended claims for which no additional fee is required.

☒ The accompanying papers include amended claims the fee for which has been calculated as follows:

CLAIMS AS AMENDED

(1)	(2) Claims remaining After amendment	(3)	(4) Highest number Previously paid for		(5) No. of Extra claims present	(6) Rate		(7) Additonal Fee
Total Claims	63	Minus	41	=	22	x $18	=	$ 396.00
Indep. Claims	2	Minus	11	=	0	x $80	=	0.00
☐ First Appearance of a multiple dependent claim						+ $270	=	0.00
					Total Additional Fee for this Amendment			$396.00

* If the entry in column 2 is less than the entry in column 4, write "0" in column 5.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, write "20" in this space.
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, write "3" in this space.
The "Highest No. Previously Paid For" (Total or Indep.) is the highest number found in the appropriate box in Col 1. of a prior amendment or the number of claims originally filed.

☐ The following other fees are incurred by the accompanying papers.

☐ Other: _____

Please charge Deposit Account No. 01-0519 in the name of Amgen Inc. in the amount of $ 1,286.00. A duplicate copy of this petition is attached.

☒ If an additional extension of time is required, please consider this a request therefore.

☒ The Commissioner is hereby authorized to charge any additional fees which may be required by the accompanying papers, or credit any overpayment to Deposit Account No. 01-0519.

Please Send Future Correspondence To:
US Patent Operations/RBW
Dept. 4300, M/S 27-4-A
AMGEN INC.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

Robert B. Winter
Attorney/Agent for Applicant(s)
Registration No.: 34,458
Phone: (805) 447-2425
Date: June 28, 2001

EXPRESS MAIL CERTIFICATE

"Express Mail" mail labeling number: EL360690310US Date of Deposit: June 28, 2001

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to Box Amendment, Assistant Commissioner for Patents, Washington, D.C. 20231.

Sherry St. Andrew
Printed Name

Signature

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Boyle, William J.

Serial No.: 09/211,315 Group Art Unit No.: 1647

Filed: December 14, 1998 Examiner: Turner, S.

For: Osteoprotegerin Binding Proteins

Docket No.: A-451J

RESPONSE AND AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This is in response to the Office Action dated January 3, 2001 in which Claims 37-49 are rejected under 35 U.S.C. 112, first paragraph and 35 U.S.C. 102(a). Reconsideration and withdrawal of the rejections are requested in view of the remarks set forth below.

AMENDMENT

Please amend the application as follows:

In the claims:

Please replace Claim 42 with the following:

42. The method of Claim 38 wherein the antibody is a human antibody or fragment thereof.

Please add the following claims:

50. The method of Claim 37 wherein the antibody or fragment thereof binds to a membrane associated form of osteoprotegerin binding protein.

EXPRESS MAIL CERTIFICATE

"Express Mail" mail labeling number: EL360690310US Date of Deposit: June 28, 2001

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to Box Amendment, Assistant Commissioner for Patents, Washington, D.C. 20231

Sherry St. Andrew
Printed Name

Signature

51. The method of Claim 37 wherein the antibody or fragment thereof binds to a soluble osteoprotegerin binding protein.

52. A method of inhibiting osteoclastogenesis in a mammal comprising administering a modulator of an osteoprotegerin binding protein, wherein the modulator is an antibody or fragment thereof which binds an osteoprotegerin binding protein.

53. The method of Claim 52 wherein the antibody or fragment thereof is an antagonist antibody.

54. The method of Claim 52 wherein the antibody is a monoclonal antibody or fragment thereof.

55. The method of Claim 52 wherein the antibody is a recombinant antibody or fragment thereof.

56. The method of Claim 52 wherein the antibody is a chimeric antibody or a CDR-grafted antibody.

57. The method of Claim 52 wherein the antibody is a human antibody or fragment thereof

58. The antibody or fragment of Claim 57 which is prepared by immunization of a transgenic animal capable of producing human antibodies.

59. The method of Claim 52 wherein the antibody or fragment thereof binds to an epitope on the extracellular domain or to an epitope on a fragment of the extracellular domain of an osteoprotegerin binding protein.

60. The antibody or fragment of Claim 59 wherein the epitope comprises the BB' loop of an osteoprotegerin binding protein.

61. The antibody or fragment of Claim 59 wherein the epitope comprises the EF loop of an osteoprotegerin binding protein.

62. The method of Claim 52 wherein the antibody or fragment thereof binds to a membrane associated form of osteoprotegerin binding protein.

63. The method of Claim 52 wherein the antibody or fragment thereof binds to a soluble osteoprotegerin binding protein.

64. The method of Claim 52 wherein the antibody or fragment further comprises a composition comprising a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative and/or adjuvant.

65. (new) The method of any of Claims 52-64 further comprising administering a bone morphogenic factor selected from the group consisting of BMP-1 to BMP-12, transforming growth factor-β, a transforming growth factor-β family member, a fibroblast growth factor selected from the group consisting of FGF-1 to FGF-10, an interleukin-1 inhibitor, a TNFα inhibitor, parathyroid hormone, an E series prostaglandin, a bisphosphonate, or a bone-enhancing mineral.

66. The method of any of Claims 52-64 wherein osteoclastogenesis is associated with a condition selected from the group consisting of osteoporosis, osteomyelitis, hypercalcemia, osteopenia brought on by surgery or steroid administration, Paget's disease, osteonecrosis, bone loss due to rheumatoid arthritis, periodontal bone loss, osteopenia due to immobilization, prosthetic loosening and osteolytic metastasis.

REMARKS / ARGUMENTS

The Claims

Claims 37-49 are currently pending in the application. Claim 42 has been amended to correct the antecedent basis and does not narrow or limit the scope thereof.

New claims 50-66 have been added. Claims 50 and 51 recite an antibody which binds a membrane associated or soluble osteoprotegerin binding protein (hereafter "OPGbp"). Support for these claims is found, for example, at p. 22, lines 20-25 of the specification. Claims 52-66 recite a method of inhibiting osteoclastogenesis by administering a modulator of OPGbp wherein the modulator is an antibody which binds OPGbp. Support for these claims are found, for example, at p. 18, lines 6-10 of the specification. No new matter has been introduced nor any new issues raised which would require further consideration and/or search. Entry of the amendment and new claims is respectfully requested.

Rejection under 35 U.S.C. 112

Claims 37-49 stand rejected under 35 U.S.C. 112, first paragraph, as the specification allegedly fails to enable the subject matter of the claims. The grounds for rejection presently set forth are nearly identical to those in the Office Action of February 24, 2000 (Paper No. 11).

The rejection should be withdrawn for the following reasons:

1) It fails to establish a *prima facie* case of nonenablement because there is no evidence or reasoning as to why the specification does not enable one to make and use the claimed subject matter; and

2) It fails to respond to or even acknowledge the arguments and evidence presented in the responses of August 18, 2000 and December 6, 1999, including evidence presented in a declaration.

In order to make a rejection for lack of enablement, the initial burden is on the Examiner to explain why the disclosure fails to enable the claimed invention and to back up such assertions with acceptable evidence or reasoning. *In re Marzochi* 169 USPQ2d at 370. No such evidence or reasoning has been presented.

The Examiner's position can be summarized on p. 4 of the present Office Action:

> The method instantly claimed is not enabled because contrary to applicants assertion the specification has not taught how to identify, predict or screen for those antibodies which not only bind to OPGbp, but modulate OPGbp activity such that bone resorption is inhibited.

Applicant maintains that Example 11, even though it is a prophetic example, teaches one how to identify and screen for anti-OPGbp antibodies. Example 11 describes various OPGbp peptides and polypeptides that may be used as immunogens, including peptides from the BB' loop and the EF loop regions of OPGbp which may be important for activity of OPGbp. Also taught in Example 11 are immunization protocols for raising antibodies in both mice and rabbits, enzyme linked immunosorbent assays (EIAs) for screening antibodies for binding to a selected OPGbp antigen, and cell fusion techniques for preparing hybridomas and monoclonal antibodies. Using the teachings in the specification of the BB' and EF loops of OPGbp, one skilled in the art would be able to generate antibodies which would inhibit OPGbp activity. Thus there is sufficient guidance in the specification for obtaining the claimed invention.

In addition to teaching how to obtain anti-OPGbp antibodies, the specification also teaches how to identify those antibodies which inhibit osteoclast formation and bone resorption. Example 8 describes an assay showing an increase in osteoclastogenesis by OPGbp. Example 9 describes an assay showing an increase in bone resorption by OPGbp. One skilled in the art could readily add an anti-OPGbp antibody to one or both of the assays in order to determine the effects of an antibody on either osteoclastogenesis and/or bone resorption. Moreover, the specification at p. 18, line 6 clearly contemplates adding antibodies to these assays in order to test their effects on OPGbp activity.

The Examiner has failed provide any reasoning as to why Examples 8, 9 and 11, and other relevant sections of the specification fail to enable the claimed methods. The only argument advanced by the Examiner is that there are no working examples of anti-OPGbp antibodies. However, there is no evidence that working examples of anti-OPGbp antibodies are required for enablement, especially given the extensive guidance and direction in the specification for making and using such antibodies combined with the knowledge of one skilled in the art in preparing antibodies.

It is also argued that the quantity of experimentation to identify antibodies which bind and inhibit bone resorption would result in undue experimentation. There is no indication whatsoever of what quantity of experimentation would be undue and no evidence presented which would suggest that the identification of anti-OPGbp antibodies which inhibit osteoclastogenesis or bone resorption would require any amount of experimentation that is undue. In making this allegation, the Examiner again ignores the teachings of the specification.

Even assuming for the sake of argument that a *prima facie* case of nonenablement could be established, the Examiner has failed to address any of the evidence in rebuttal presented by Applicant, in particular the evidence presented in the response of August 18, 2000.

Applicants reiterate the arguments and evidence presented on the record to date and specifically point out that evidence which has been presented in rebuttal and ignored by the Examiner:

The Examiner has ignored two references provided by the Applicant to rebut the Examiner's allegation that the art is unpredictable with respect to the generation of antagonist antibodies. The references are Yamamato et al. (Microbiol. Immunol. 32, 339-350 (1988)) and Siegel et al. (Cytokine 7, 15-25 (1995)) which described inhibitory antibodies to γ-interferon and tumor necrosis factor α (TNF-α), respectively. In both cases, the references showed that the mechanism for inhibition was the ability of antibodies to block binding of γ-interferon or TNF-α to its corresponding receptor.

The Examiner has ignored the relevant sections of the Federal Circuit's decision in *Wands* which clearly states that generating antibodies to a given immunogen and the testing of those antibodies is well within the level of skill in the art absent any evidence to the contrary. In the present case, there has been no evidence presented that generating anti-OPGbp antibodies and testing said antibodies for their ability to block OPGbp binding to its receptor and the ability to block osteoclast formation could not be carried out by one skilled in the art without undue experimentation.

The Examiner has ignored the Declaration of John K. Sullivan which showed that one skilled in the art could obtain anti-OPGbp antibodies which block osteoclast formation without undue

experimentation. The antibodies disclosed in the declaration were generated by using materials and methods substantially disclosed in the application. Yet, in the subsequent communication, the declaration was not even mentioned and the rejection was maintained on identical grounds. It is a clear error to dismiss a declaration of a person skilled in the art without adequate explanation of how the declaration failed to overcome the alleged *prima facie* case for rejection. *In re Alton* 37 USPQ2d 1578 (Fed. Cir. 1996)

In view of the remarks above, the rejection under 35 U.S.C. 112, first paragraph, should be withdrawn.

Rejection under 35 U.S.C. 102

Claims 37 and 38 are rejected under 35 U.S.C. 102(a) as being anticipated by Tsukii et al. (Biochem. Biophys. Res. Comm 246, 337-341 (1998) as evidenced by Takahashi et al. (cited in connection with the 112 rejection above). The Examiner notes the polyclonal antibody referenced in the abstract on p. 337, the text on p. 339, and Figures 2 and 3 of the Tsukii reference. Reconsideration is requested.

The rejection under 102(a) is incorrect. Section 102(a) states in part that a patent shall not be granted if the invention was patented or described in a printed publication "before the invention thereof by the applicant". The Tsukii reference cited under this section has a publication date of May 8, 1998 as evidenced by copies of the title page and table of contents attached hereto as Exhibit A. The present application has a filing date of June 23, 1997 and claims priority to U.S. Serial No. 08/842,842 filed on April 16, 1997. The Tsukii reference was published more than one full year after the Applicant's priority date and consequently cannot be prior art under 102(a). It is requested that the rejection be withdrawn.

CONCLUSION

Upon entry of the new claims, Claims 37-66 are in condition for allowance and an early notice thereof is solicited.

Respectfully submitted,

Robert B. Winter
Attorney/Agent for Applicant(s)
Registration No.: 34,458
Phone: (805) 447-2425
Date: June 28, 2001

Please send all future correspondence to:

U.S. Patent Operations/RBW
Dept. 4300, M/S 27-4-A
AMGEN INC.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

VERSION WITH MARKINGS TO SHOW CHANGES MADE

42. (amended) The [composition] method of Claim 38 [which comprises] wherein the antibody is a human antibody or fragment thereof.

Exhibit A

Volum 246, Number 1, May 8, 1998 **BBRC**

CONTENTS

AUTHOR INDEX, Volume 246, Number 1, May 8, 1998		vi
BREAKTHROUGHS AND VIEWS		
Genes for Sexual Behavior	**Daisuke Yamamoto and Yoshiro Nakano**	1
REGULAR ARTICLES		
Patent Ductus Arteriosus and Neonatal Death in Prostaglandin Receptor EP4-Deficient Mice	**Eri Segi, Yukihiko Sugimoto, Atsushi Yamasaki, Yoshiya Aze, Hiroji Oida, Tatsuya Nishimura, Takahiko Murata, Toshiyuki Matsuoka, Fumitaka Ushikubi, Masaya Hirose, Takashi Tanaka, Nobuaki Yoshida, Shuh Narumiya, and Atsushi Ichikawa**	7
Prompt Activation of Telomerase by Chemical Carcinogens in Rats Detected with a Modified TRAP Assay	**Masayoshi Miura, Yuji Karasaki, Tetsuya Abe, Ken Higashi, Kunio Ikemura, and Sadao Gotoh**	13
Genetic Structure of the *bphG* Gene Encoding 2-Hydroxymuconic Semialdehyde Dehydrogenase of *Achromobacter xylosoxidans* KF701	**Eunja Kang, Jeong Mi Oh, Jeongrai Lee, Young-Chang Kim, Kyung-Hee Min, Kyung Rak Min, and Youngsoo Kim**	20
Role of Latent TGF-β1 Binding Protein in Vascular Remodeling	**Tetsuto Kanzaki, Ritsuko Shiina, Yasushi Saito, Hideya Oohashi, and Nobuhiro Morisaki**	26
Occurrence of Pyridoxal 5′-Phosphate-Dependent Serine Racemase in Silkworm, *Bombyx mori*	**Takuma Uo, Tohru Yoshimura, Susumu Shimizu, and Nobuyoshi Esaki**	31
Identification of a Recurrent Missense Mutation in the Norrie Disease Gene Associated with a Simplex Case of Exudative Vitreoretinopathy	**Barkur S. Shastry**	35
Identification of a Potential Substrate Binding Domain in the Mammalian Peptide Transporters PEPT1 and PEPT2 Using PEPT1-PEPT2 and PEPT2-PEPT1 Chimeras	**You-Jun Fei, Jin-Cai Liu, Takuya Fujita, Rong Liang, Vadivel Ganapathy, and Frederick H. Leibach**	39
Different Biochemical Properties of Nuclear and Microsomal Estrone-3-Sulfatases: Evidence for the Presence of a Nuclear Isozyme	**Bao Ting Zhu, Jia-Huey Fu, Shiyao Xu, Frederick C. Kauffman, and Allan H. Conney**	45
Novel CRE-Binding Proteins of 11–16 kDa Bind to the LDH A-Gene CRE in a Sequence Specific and Hepatocyte-Growth Dependent Manner in Partially Hepatectomized Rat Liver	**Mi Young Lee, Eun Sook Hwang, and Seung Ki Lee**	50

Continued

Abstracted/Indexed in Biological Abstracts (BIOSIS), Chemical Abstracts, Current Contents/Life Sciences, EMBASE, *Index Medicus* (MEDLINE), Science Citation Index, and SCISEARCH

EXHIBIT C

LB → RBW

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/211,315	12/14/98	BOYLE N	A-451

EXAMINER
TURNER, S

021069
AMGEN INCORPORATED
MAIL STOP 27-4-A
ONE AMGEN CENTER DRIVE
THOUSAND OAKS CA 91320-17

HM12/0731

ART UNIT	PAPER NUMBER
1647	21

DATE MAILED: 07/31/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Advisory Action

Application No.	Applicant(s)
09/211,315	Boyle
Examiner	**Art Unit**
Sharon L. Turner, Ph.D.	1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 7-28-01 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

a) ☒ The period for reply expires 6 months from the mailing date of the final rejection.

b) ☐ In view of the early submission of the proposed reply (within two months as set forth in MPEP § 706.07 (f)), the period for reply expires on the mailing date of this Advisory Action, OR continues to run from the mailing date of the final rejection, whichever is later. In no event, however, will the statutory period for the reply expire later than SIX MONTHS from the mailing date of the final rejection.

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will be entered upon the timely submission of a Notice of Appeal and Appeal Brief with requisite fees.

3. ☒ The proposed amendment(s) will not be entered because:

   (a) ☒ they raise new issues that would require further consideration and/or search. (See NOTE below);

   (b) ☐ they raise the issue of new matter. (See NOTE below);

   (c) ☒ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☒ they present additional claims without cancelling a corresponding number of finally rejected claims.

   NOTE: *The proposed amendment changes the dependency of claim 42 requiring new search and considerations. Newly presented claims 50-66 have not been previously searched or considered on the merits.*

4. ☐ Applicant's reply has overcome the following rejection(s): _____

5. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in separate, timely filed amendment cancelling the non-allowable claim(s).

6. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because:
The proposed amendment has not been entered. All rejections are maintained for the reasons of record.

7. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

8. ☒ For purposes of Appeal, the status of the claim(s) is as follows (see attached written explanation, if any):

   Claim(s) allowed: _____

   Claim(s) objected to: _____

   Claim(s) rejected: *37-49*

9. ☐ The proposed drawing correction filed on _____ a) ☐ has b) ☐ has not been approved by the Examiner.

10. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____.

11. ☐ Other:

CHRISTINE J. SAOUD
PRIMARY EXAMINER
Christine J. Saoud

Attachment for PTO-948 (Rev. 03/01, or earlier)
6/18/01

The below text replaces the pre-printed text under the heading, "Information on How to Effect Drawing Changes," on the back of the PTO-948 (Rev. 03/01, or earlier) form.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the Notice of Allowability. Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136(a) or (b) for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit the drawing corrections within the time period set in the attached Office communication. See 37 CFR 1.85(a).

Failure to take corrective action within the set period will result in **ABANDONMENT** of the application.

EXHIBIT D

LB - RBW

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

C

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/211,515	12/14/98	BOYLE	A-451-XJ

EXAMINER: TURNER, S

ART UNIT	PAPER NUMBER
1647	22

DATE MAILED: 08/14/01

OIPE SCI73
NOV 28 2001
PATENT & TRADEMARK OFFICE

21069
AMGEN INCORPORATED
MAIL STOP 27-4-A
ONE AMGEN CENTER DRIVE
THOUSAND OAKS CA 91320-1799

HM22/0814

DOCKETED
Pet. to Revive
10/14/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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PATENT OPERATIONS
AMGEN

PTO-90C (Rev. 2/95)
*U.S. GPO: 2000-473-000/44602

2 - Mail Copy

Notice of Abandonment

Application No.	Applicant(s)
09/211,315	Boyle
Examiner	**Art Unit**
Sharon L. Turner, Ph.D.	1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

This application is abandoned in view of:

1. ☒ Applicant's failure to timely file a proper reply to the Office letter mailed on 7-31-01.

   (a) ☐ A reply was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply (including a total extension of time of ____ month(s)) which expired on _____.

   (b) ☐ A proposed reply was received on _____, but it does not constitute a proper reply under 37 CFR 1.113(a) to the final rejection.

   (A proper reply under 37 CFR 1.113 to a final rejection consists only of: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114).

   (c) ☒ No response has been received.

2. ☐ Applicant's failure to timely pay the required issue fee and publication fee, if applicable, within the statutory period of three months from the mailing date of the Notice of Allowance (PTOL-85).

   (a) ☐ The issue fee and publication fee, if applicable, was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the statutory period for payment of the issue fee (and publication fee) set in the Notice of Allowance.

   (b) ☐ The submitted issue fee of $_____ is insufficient. A balance of $_____ is due.

   The issue fee required by 37 CFR 1.18 is $_____. The publication fee, if required by 37 CFR 1.18(d) is $_____.

   (c) ☐ The issue fee and publication fee, if applicable, has not been received.

3. ☐ Applicant's failure to timely file new formal drawings as required by, and within the three-month period set in, the Notice of Allowability (PTO-37).

   (a) ☐ Proposed new formal drawings were received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply.

   (b) ☐ The proposed new formal drawings filed on _____ are not acceptable and the period for reply has expired.

   (c) ☐ No proposed new formal drawings have been received.

4. ☐ The letter of express abandonment which is signed by the attorney or agent of record, the assignee of the entire interest, or all of the applicants.

5. ☐ The letter of express abandonment which is signed by an attorney or agent (acting in a representative capacity under 37 CFR 1.34(a)) upon the filing of a continuing application.

6. ☐ The decision by the Board of Patent Appeals and Interferences rendered on _____ and because the period for seeking court review of the decision has expired and there are no allowed claims.

7. ☐ The reason(s) below:

CHRISTINE J. SAOUD
PRIMARY EXAMINER
Christine J. Saoud

Attachment for PTO-948 (Rev. 03/01, or earlier)
6/18/01

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